

The Process of Leukemogenesis

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Leukemias are monoclonal diseases that arise from cells in the hematopoietic stem and progenitor cell compartment. Consistent with emerging models of carcinogenesis, leukemogenesis is an evolutionary process that involves multiple independent genetic and epigenetic events. Over the last half-century a predominant paradigm has emerged to describe leukemia developing secondary to alkylating drug therapy or exposure to benzene in which progressive dysplastic changes, accompanied by a distinct pattern of clonal cytogenetic abnormalities, give rise to acute myelogenous leukemia. Characterization of these clonal chromosomal aberrations, together with observed alterations in other growth-promoting genes, provides a useful framework for studying chemical leukemogenesis and for use in understanding the origins and development of leukemia in general. — Environ Health Perspect 104(Suppl 6):1239–1246 (1996)

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Process of Leukemogenesis

Leukemias are monoclonal diseases that originate from individual cells in the bone marrow. Like other cancers, leukemias often exhibit a progression in their natural history from cells that possess a phenotype exhibiting some remnant of normal differentiation to the progressive loss of maturation ability and the development of an aggressive undifferentiated malignant phenotype (1). A common characteristic of malignant neoplasms, including leukemias, is abnormal regulation of cell growth. A particular challenge to understanding the role of altered regulation of cell growth in the development of leukemia is that differences in the behavior between normal and malignant hematopoietic cells are often subtle. For example, normal hematopoietic progenitor cells possess some characteristics common to malignant cells, among them: the ability to proliferate, survive intravascular transit, and transmigrate

into tissues, and the ability to grow in semisolid media. On the other hand, leukemic cells often do not exhibit total growth-factor independence when first introduced into culture.

Consistent with present models for the origin and progression of neoplasia, leukemia development has long been thought to be a multistep process. Foulds first proposed a multistep progression in which a normal cell must pass through a number of distinct intermediate stages before a frank malignancy develops (2,3). Since that time, a variety of independent observations have emerged to support the conclusion that cancer in general is an evolutionary process in which multiple events involving independent genetic alterations in protooncogenes or suppressor genes together with epigenetic or environmental factors contribute to the development of the full malignant phenotype (4,5). The

best understood example of carcinogenesis in a normal, rapidly proliferating tissue is carcinoma of the colon, in which it appears that as many as five independent genetic and epigenetic changes may be required for the progression of a normal epithelial cell to a carcinoma cell (6,7) (Figure 1). This model is based on the seminal observation by Vogelstein et al. that the incidence of *ras*-gene mutations increased dramatically as a function of the size and malignant phenotype of the tumor and that four molecular alterations accumulated in a manner that paralleled the clinical and histopathological progression of the tumor (7). In addition to illustrating the multifactorial nature of cancer development, these correlative studies reveal that the precise sequence of events is not a constant but that individual tumors can vary in their evolution.

Regulation of Hematopoiesis

A great deal of evidence suggests that proto-oncogenes and other growth-promoting genes such as those encoding for cytokines or their receptors play an important role in carcinogenesis and malignant transformation. Recent advances in cell and molecular biology have revolutionized our understanding of the regulation of growth in normal hematopoiesis. Therefore, a brief summary of the functions of cytokines in regulating normal hematopoiesis provides a logical foundation for a discussion of the mechanisms of altered cell growth and differentiation occurring in leukemogenesis. Three fundamental cellular processes that define hematopoietic cells are survival, proliferation, and differentiation. The survival and proliferation of hematopoietic progenitor cells (HPC) are controlled by multiple growth factors or cytokines with overlapping functions that act individually or in combination to regulate hematopoiesis (8). Recent studies support the conclusion that either interleukin-3 (IL-3) or granulocyte/macrophage-colony-stimulating factor (GM-CSF) are required to sustain the viability of stem cells or early HPC. Early HPC can also be recruited into active cycle in response to these same cytokines or a second stimulus such as *c-kit* ligand (CKL), IL-6, or granulocyte colony-stimulating factor (G-CSF) (9–11). Later committed progenitor cells are controlled by lineage-specific cytokines such as erythropoietin, macrophage colony-stimulating factor (M-CSF), G-CSF, and IL-5. Populations of

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Abbreviations used: AML, acute myelogenous leukemia; β 2AR, β 2-adrenergic receptor; CKL, *c-kit* ligand; CML, chronic myelogenous leukemia; ECGF, endothelial cell growth factor; EGR1, early growth response 1; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte/macrophage colony-stimulating factor; HPC, hematopoietic progenitor cells; IL, interleukin; M-CSF, macrophage colony-stimulating factor; MDS, myelodysplastic syndrome; PDGFR, platelet-derived growth factor receptor; Rb, retinoblastoma; s, secondary.

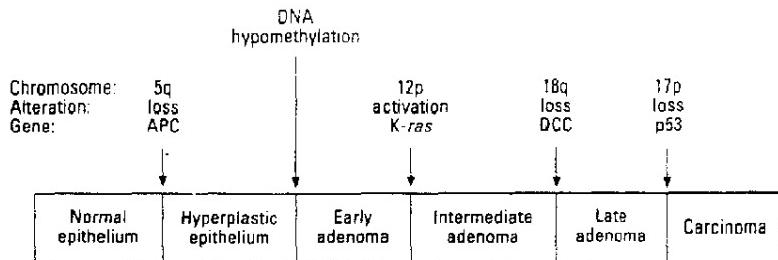


Figure 1. Changes that occur during the evolution of a typical colorectal carcinoma. Schematic representation of a model of tumor progression in which independent steps are required, leading to the activation of at least one protooncogene coupled with the successive loss of several tumor suppressor genes. Adapted from Varmus and Weinberg (6).

early HPC responding to IL-3 and GM-CSF exhibit extensive overlap. Although IL-3 or GM-CSF is required to sustain survival of early dormant progenitor cells (12), IL-3 apparently stimulates cells at an earlier stage of differentiation than GM-CSF (13). Early IL-3 responding populations support the development of T- and B- lymphocyte progeny as well as myeloid and erythroid lineages (14–16). Because IL-3 responsiveness is a characteristic of HPC at multiple levels of differentiation, HPC responsive to GM-CSF may represent a subpopulation of multipotential cells that respond to IL-3 (17). The processes that govern differentiation of HPC are less well understood and are thought by many to be governed via stochastic mechanisms. Nevertheless, it is reasonable to infer that differentiation and lineage commitment are at least indirectly influenced by environmental factors (e.g., cytokines). The role of altered regulation of cytokine expression/response in leukemogenesis is complex, with consistent enhanced expression of GM-CSF or IL-3, resulting in profound myelodysplastic changes (18–20). Altered regulation of clonogenic response to GM-CSF features prominently in both human and murine myeloproliferative disorders and is a frequent early observation in the development of acute myelogenous leukemia (AML) (5,21). Repeated exposure of mice to benzene *in vivo* enhances GM-CSF response (22), and chronic exposure to high concentrations induces a persistent myeloproliferative disorder (23,24). Moreover, the benzene metabolite, hydroquinone, selectively enhances clonogenic response to GM-CSF in murine and human bone marrow cells (25–27). To date, alterations in expression of M-CSF/FMS have not yet been shown to result in abnormal myeloid proliferation.

Relationship between Leukemia, Preleukemia, and Myelodysplastic Syndrome

It is generally recognized that chromosomal aberrations or deletions can alter the regulation and function of protooncogenes and other growth-promoting genes. This, together with our growing knowledge of the function and role of cytokines, their receptors, protooncogenes, and suppressor genes, provides a useful framework for analysis of the respective roles of altered cell growth and differentiation in chemical leukemogenesis. To this end, an impressive literature exists that describes the natural history of leukemia secondary to alkylating drug or occupational exposure in which the development of AML is *a*) preceded by progressive dysplastic or "preleukemic" changes, and *b*) accompanied by a distinct pattern of clonal cytogenetic abnormalities.

The concept of preleukemia originated around the turn of the century with the observation that AML could be preceded by a cytopenic dysplasia involving one or more hematopoietic cell lines (28). However, preleukemia was not generally accepted as a clinical entity until the widespread introduction of radiation and chemotherapy in the treatment of other types of cancer. It is now widely recognized that persistent cytopenias and other blood dyscrasias, including dyserythropoiesis, dysgranulopoiesis, and dysmegakaryopoiesis, frequently precede the onset of leukemia in patients developing AML secondary to exposure to benzene or alkylating agents (1,29–32). Over the past decade the term preleukemia has been largely supplanted by the more functional classification of the myelodysplastic syndromes (MDS) by the fast atom bombardment (FAB) (33). Differences in growth and differentiation between MDS and

AML find analogy in the progression of solid tissue tumors from metaplasia and dysplasia to carcinoma. This observation, together with the frequent progression of secondary s-MDS to frank AML, leads to the inescapable conclusion that MDS and AML should be considered a single disease continuum when viewed in the context of chemical leukemogenesis.

As a secondary malignancy, AML clearly dominates the leukemia literature. At present, the world literature contains approximately 38,000 cases of individuals treated with alkylating agents or radiation for primary malignancies or immune disorders that have been followed for development of secondary malignancies, the most prominent of which is AML. These typically involve M1, M2, M4, M6, but not M3 or M5 subtypes of AML, based on the FAB classification system (34,35). From these studies at least 1322 cases of AML and 320 cases of MDS have been reported (29,30,36–57). If one includes all cases attributed to solvent exposure in general or benzene specifically, whether anecdotal or reported in case-control or cohort studies, the total number of secondary leukemias approaches 2100, over 96% of which are MDS/AML (44,58–70). The frequency of secondary AML/MDS varies markedly depending on individual therapeutic regimen but historically has ranged between 0.6 and 17%, with relative risks averaging about 100-fold (range 9–320 X). These studies establish a consistent and very strong pattern in which the development of AML is preceded by a period of preleukemia in 33 to 80% of the cases and is accompanied by clonal cytogenetic abnormalities involving loss of all or part of chromosomes 5 and 7 (Table 1). On average the frequency of deletions or loss of chromosomes 5 and 7 in studies of patients who develop MDS or AML after antineoplastic therapy ranges between 85 and 95% (71–76). The same cytogenetic abnormalities occur much less frequently in *de novo* AML: in 660 *de novo* cases chromosomes 5 and 7 were observed in 4.2 and 4.4%, respectively, and simultaneously in 3.2% (77,78). Consistent with the evolution of s-AML described previously, most patients presenting with clonal chromosomal aberrations involving the loss of all or part of chromosomes 5 or 7 exhibit a preleukemic phase prior to the onset of AML (79). Analysis of the specific pattern of cytogenetic involvement in AML developing secondary to benzene exposure is complicated by the ambiguities commonly associated with the characterization of

Table 1. Cytogenetic characteristics of secondary acute myelogenous leukemia

Study	Clonal aberrations		-5q- / 5q+ / 5q- / 5q+	
	De novo AML, %	Secondary AML, %	De novo AML, %	Secondary AML, %
PiWOL (77)	54	73	12	48
Le Beau et al. (73)	56	97	16	87
Rowley et al. (72)	-	96	-	92
Rowley et al. (71)	-	100	-	90
Pedersen-Bjergaard et al. (72)	-	86	-	89
Wald and Conner (122)	-	87	-	80
Mitelman et al. (59)	24	83	12	84
Golomb et al. (60)	-	75	-	67
Fagioli et al. (61)	29	88	20	46

exposure in occupational and retrospective studies. Issues related to the specificity and intensity of benzene exposure notwithstanding, the classic pattern involving a high frequency of loss of all or part of chromosomes 5 and/or 7 is also observed in studies of patients occupationally exposed to benzene specifically or solvents among which benzene is the only recognized leukemogen (58–61,63,65,80,81). The consistency of this pattern is all the more impressive when one considers that the association between exposure and cytogenetic abnormalities in occupational studies is invariably diluted; i.e., studies providing the greatest detail on cytogenetic abnormalities are weakest in the characterization of exposure criteria. Independently, recent studies of peripheral lymphocytes in benzene-exposed individuals in China have shown that benzene exposure induces aneuploidy of G-group chromosomes, with an especially strong effect on chromosome 7. Both hyper- and hypodiploidy of chromosome 7 occurred more frequently in benzene-exposed workers than in matched controls (82). Other nonrandom clonal chromosomal abnormalities, such as +8 or +21, have been observed to be increased in either exposed or nonexposed populations, depending on the study (58–60,62,81). These observations suggest that although some chromosomes other than 5 or 7 can be involved in the pathogenesis of AML secondary to exposure to benzene or chemotherapeutic alkylating agents, they are not useful in discriminating between *de novo* and s-AML (83). More recently, a distinct pattern of secondary AML has been observed following therapy with drugs targeting DNA-topoisomerase II. The pattern of AML developing as a consequence of exposure to these agents, examples of which include etoposide and teniposide, includes the notable absence of a preleukemic phase, frequent presentation of an M3 subtype, and balanced chromosome

aberrations involving bands 11q23 and 21q22 (84). Although it has been hypothesized that benzene metabolites may interfere with topoisomerase II (85), the pattern of leukemias and chromosomal aberrations typically associated with inhibition of this enzyme has yet to be observed in occupationally exposed populations.

5-/5q-: A Model for the Pathogenesis of Leukemia

The pattern of reoccurring chromosomal abnormalities associated with the development of leukemia can be used as a guide in understanding the etiology and pathogenesis

of these diseases. A number of gene loci have been mapped to chromosome 5; however, their function(s) remains largely unknown (86). However, recent progress in the mapping of genes to the region of chromosome 5 involved in s-MDS/AML provides a logical starting point for a discussion of possible mechanisms of leukemogenesis. Deletions of all or part of chromosomes 5 or 7 are the earliest clonal alterations that have been detected in MDS/AML. Deletions associated with 5q- in s-MDS/AML are usually interstitial without translocation of the deleted material (73,87). The variability of the breakpoints, together with identification of the critical region (5q31), suggests that the relevant genetic event may be the deletion of a critical gene sequence rather than consistent juxtaposition of DNA sequences that may occur in chromosome translocation (Figure 2) (73). A cluster of genes involved in the regulation of hematopoiesis is located at q31 on chromosome 5 (Figure 3). These include GM-CSF, IL-3, IL-4, IL-5, CD14 (which encodes a myeloid-specific surface molecule that has structural characteristics of a receptor), and early growth response 1 (EGR1) (an *EGR* gene with *fos*-like properties) (88).

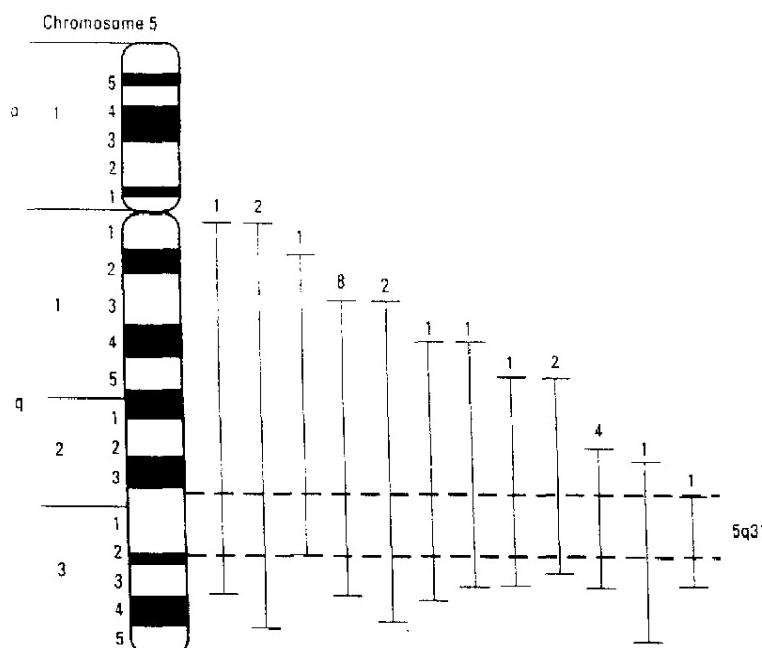


Figure 2. Fragile site on chromosome 5 associated with region of critical deletion in patients with t-AML. Vertical bars indicate deleted segments and numbers indicate number of patients with same deletion. Dashed bars indicate smallest overlapping region of 5q31. Reproduced from Rowley and Le Beau (73) with permission.

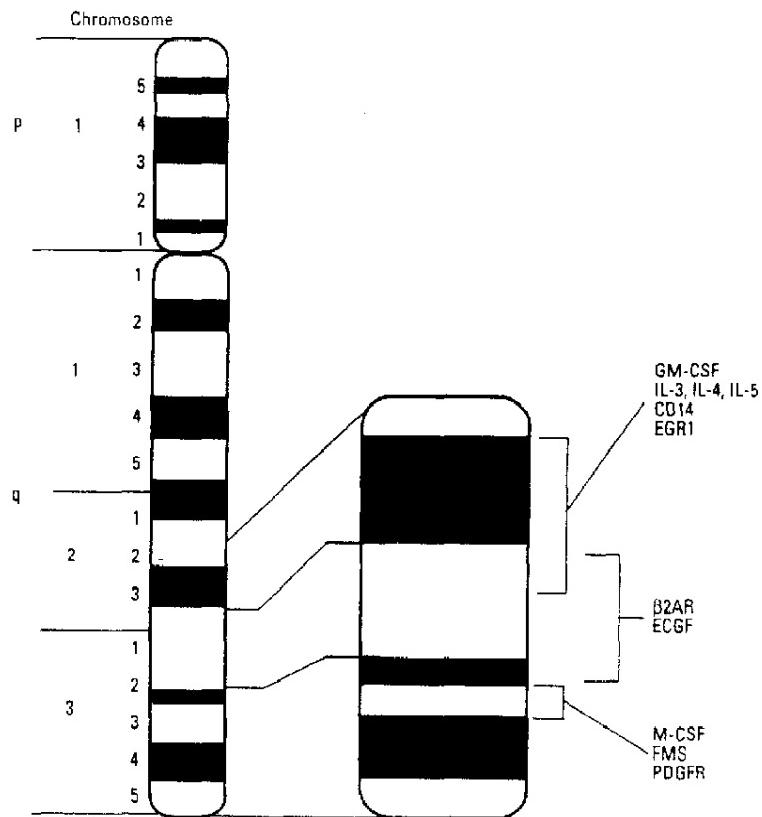


Figure 3. Genetic map of genes located in and adjacent to the 5q31—critical region deleted in patients with r-AML. Modified from Rowley and Le Beau (88). Abbreviations: B2AR, β_2 -adrenergic receptor; ECGF, endothelial cell growth factor; PDGFR, platelet-derived growth factor receptor.

There is no evidence for homozygous deletion of any of these genes in AML, such as has been described for retinoblastoma in which the absence of one allele of retinoblastoma gene is followed by a second somatic mutation, resulting in loss of both copies of the gene (89). The most consistent deletion associated with 5q31 appears to involve the loss of one allele encoding either GM-CSF or EGR1 (88). Close to, but lying outside of, the critical region is the protooncogene, *c-fms*, the receptor for M-CSF that acts exclusively on cells of monomacrophage lineage (90). Ostensibly, a critical role for *c-fms* in the development of AML is an attractive hypothesis in that it encodes a cytokine receptor. However, the weight of evidence suggests that *c-fms* is probably not involved in early events in AML development. M-CSF and *c-fms* lie outside the critical deletion region at 5q31 (88), and although FMS expression can be detected on leukemia cells in approximately 50% of

AMLs, abnormal myeloid proliferation has yet to be demonstrated as a result of inappropriate expression of M-CSF or FMS (5). Nevertheless, the incidence of point mutations in the *c-fms* gene in AML or MDS has been reported to be 13% in one series, suggesting that subtle changes in *c-fms* expression may contribute in some way to the development of the malignant phenotype (91).

At present, there are at least two molecular hypotheses for the role of 5q abnormalities in the development of MDS/AML. First is the loss of a single allele of a heretofore unidentified tumor suppressor gene that results in production of a nonfunctional protein; this would be analogous to the inactivation of p53 by point mutation. The second hypothesis is that loss of a single allele leads to altered gene dosage and a reduction in the level of gene product, such as GM-CSF. A third possibility is that involvement of intact genes adjacent to the interstitial deletion cannot at this

time be entirely excluded since their function could ostensibly be influenced by the structural changes that have occurred in the chromosome.

In addition to early involvement of genes on chromosome 5, a growing number of protooncogenes have been reported to undergo structural or functional alterations in AML with widely differing frequency. These have been the subject of a number of reviews (5,92–94). To date, no single or consistent pattern of protooncogene involvement has been associated with AML development, suggesting that multiple genes may interact via different pathways in the evolution of the disease. This discussion will focus only on a small number of these genes. The human *ras* genes encode p21 proteins that appear to play an important role as second messengers in tyrosine kinase receptor-mediated signal transduction (95). It has been hypothesized that *ras* mutations may feature prominently in the development of s-AML (96). However, what role *ras* mutations play in the development of either *de novo* or s-AML remains uncertain. In a large number of studies, *ras* protooncogene activation, principally N-RAS, has been variously reported to occur in about 25% of cases of *de novo* AML (92,95). However, clonal chromosomal aberrations have been demonstrated to precede *ras* involvement in the evolution of the disease (97,98) and, when identified, *ras* mutations tend to be present only in subclones of the leukemic cells (97,99). To date, RAS involvement has not proven to be either a prognostic indicator or to correlate with FAB subtype. From these studies it appears that *ras* mutation is an unlikely early event in AML and is insufficient to cause the disease. However, *ras* activation can occur at a number of stages in the development of AML and it cannot be excluded that RAS may play a role in the evolution or progression of at least some cases of AML (100). The p53 gene encodes a phosphoprotein nuclear transcription factor that is spatially regulated within the cell during the cell cycle. The wild-type protein is known to limit cell growth apparently by two independent mechanisms: mediating apoptosis and as a checkpoint, regulating the length of G1 (101). Often referred to as a tumor suppressor gene, inactivation of p53 is an important event in the transformation of many tumors and is the most frequently encountered gene mutation in human cancer (102). Inactivation of p53 is involved in the progression to blast crisis in

20 to 30% of chronic myelogenous leukemia (CML) cases, but it is only encountered in a few percent of MDS/AML cases (103). Within this small subset of AMLs, p53 inactivation is a late event and is apparently associated with loss of a differentiated cell phenotype, aggressive course, and a poor prognosis. The retinoblastoma (Rb) gene was the first identified tumor suppressor gene and like p53 encodes a phosphonuclear protein that is involved in regulating critical events in the cell cycle (104,105). Absent or decreased expression of Rb protein is observed in approximately 30% of AML cases and is associated with a particularly dismal response to therapy (106,107).

A Model for Leukemogenesis

Up to this point the discussion has focused exclusively on the role of clonal hematopoietic stem and progenitor cell abnormalities in the development and evolution of MDS/AML. Another hypothesis has been proposed in which altered growth factor production by fibroblasts, endothelial cells, and macrophages may feature prominently in the development of leukemias (108). As the basis for a stand-alone theory of leukemogenesis, each of these alternatives possesses individual strengths and weaknesses. A diverse set of observations argues persuasively that the ultimate clonal derivation of most cases of AML and MDS are HPC essentially restricted to the myeloid lineage (109–112). Superficially, a clonal lesion would appear to be incompatible with the notion that persistent and progressive myeloproliferative disease could arise as a consequence of altered microenvironmental influences that are ostensibly independent and oligoclonal. On the other hand, how allelic deletion of a cytokine gene such as GM-CSF in a single clone of progenitor cells can predispose to a series of events that ultimately leads to AML remains a niggling enigma. The basis for the argument for a stromal origin is that multiple peripheral cytopenias and dysplasias are the rule rather

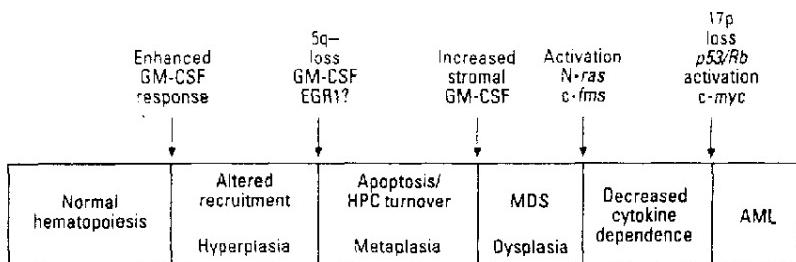


Figure 4. Hypothetical model for the evolution of secondary leukemia involving 5q-. Schematic representation of a model of abnormal myeloproliferative progression in which early events, including alterations in cytokine response and loss of heterozygosity (5q-), are followed by activation of at least one protooncogene coupled with the successive loss of a tumor suppressor gene.

than the exception in the evolution of s-AML, and abnormal cytokine production is frequently encountered in cases of MDS/AML (113–116).

Alternatively, one can propose an integrative model of leukemogenesis that is compatible with both clonal and microenvironmental involvement in the development and progression of these myeloproliferative disorders. In hematopoiesis, there is considerable evidence that cell viability and cell growth are functions that can be dissociated (117). Raza et al. (118,119) have recently reported an increase in both cell turnover and apoptosis in bone marrow of patients with MDS relative to normal bone marrow that is in sharp contrast to AML, in which proliferation is high but the frequency of apoptotic cells is low. A chromosomal aberration in an early progenitor cell could result in allelic deletion of one GM-CSF gene, resulting in a commensurate decrease in intracellular GM-CSF. Using antisense technology, Pech and co-workers provide evidence that low-level autocrine regulation of GM-CSF may regulate survival in early progenitor cells independent of exogenous GM-CSF that is associated with proliferation (120). If intracellular GM-CSF were insufficient to suppress apoptosis in maturing cells of the affected clone, a corresponding increase in

exogenous GM-CSF occurring in physiologic response to increased apoptosis would drive cell proliferation, leading to an increase in overall cell turnover in the affected clone. This model is consistent with the regulatory paradox in MDS in which bone marrow hyperplasia is accompanied by ineffective hematopoiesis and cytopenias. Subsequent events involving genes linked directly or indirectly to cell survival and maturation (e.g., *ras*, p53, or Rb) could enable the escape of the subclone from the apoptotic treadmill and development of a frank AML (Figure 4).

This model is only one possible explanation for the origins and progression of leukemia that is compatible with roles for both clonal and microenvironmental events. The earliest observations associated with the development of MDS/AML suggest that a relatively small number of alternative events predispose the development of leukemia. These most likely involve a clonal chromosomal abnormality together with altered regulation of cytokine response. However, the diversity of gene involvement in later stages of AML progression is consistent with an emerging pattern in cancer biology in which multiple alternative genetic pathways converge in the development of a specific tumor type.

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